

REMARKS

Applicant notes with appreciation reasoned withdrawal of the rejections under 35 U.S.C. §102(b) over Wagner.

Claims 1-19, 21, 22, 24-27, and 30-34 are pending in the application.

Currently, claims 1-12, 14-19, 21, 22, 24-25, 27-28, 30-32, and 34 are rejected under 35 U.S.C. § 103(a) as unpatentable over Wagner et al. in view of Gygi et al. (PNAS 2000 97(17):9390-9395) and Kachman et al. (Anal. Chem. 2002 74:1779-1791).

Claims 1-6, 8-11, 13, 26, and 33 are rejected under 35 U.S.C. § 103(a) as unpatentable over Wagner et al. in view of Niliotis et al. (J. Chromotography A 2000;886:99-110).

Remarks directed to the rejection of claims 1-12, 14-19, 21, 22, 24-25, 27-28, 30-32, and 34 under 35 U.S.C. § 103(a) as unpatentable over Wagner et al. in view of Gygi et al. (PNAS 2000 97(17):9390-9395) and Kachman et al. (Anal. Chem. 2002 74:1779-1791).

Claims 1-12, 14-19, 21, 22, 24-25, 27-28, 30-32, 34 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Wagner et al. in view of Gygi et al. (PNAS 2000 97(17):9390-9395) and Kachman et al. (Anal. Chem. 2002 74:1779-1791). This rejection is respectfully traversed.

Applicant incorporates by reference all remarks of record that Wagner fails to teach or suggest all elements of claim 1 or the claims that depend therefrom. To sustain the current rejection of claims 1-12, 14-19, 21, 22, 24-25, 27-28, 30-32, and 34 under 35 U.S.C. § 103(a), Paper No. 20080721 cites Wagner as teaching all elements of the claims in a rejection under 102(b). However, as the remarks made of record October 28, 2008 make clear, Wagner fails to

to teach or suggest all elements for which it is cited. As such, reliance on Wagner is not supported and the outstanding rejection under 103(a) fails to satisfy a *prima facie* case of obviousness.

Standards for Obviousness Rejection and Response

The Supreme Court in KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007), has recently articulated the standard for establishing whether a claim is obvious over prior art. In KSR the Court reestablished that Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), remains the controlling precedent. Under Graham, to establish a *prima facie* case of obviousness an Examiner must analyze:

- (1) the scope and content of the prior art; and
- (2) the differences between the claimed invention and the prior art; and
- (3) the level of ordinary skill in the pertinent art.

Graham, 383 U.S. at 17–18, 148 USPQ at 467.

It is Applicant's understanding that the form and substance of rejections under 35 U.S.C. §103(a) are currently governed by guidelines articulated in the Federal Register, 2007, Vol. 72, No. 195, 56525-56534 therein embodying the test outlined in KSR. These guidelines require a factual inquiry, resolution of ordinary skill in the art to which the invention pertains, and an explicit recitation of the rationale for the rejection as selected from among seven possible bases (identified in the Federal Register with letters A-G). The basis for Applicant's reply is also provided within the Federal Register guidelines.

While the outstanding rejection appears to address the scope and content of the prior art and the differences between the claimed invention and the prior art, the level of ordinary skill in

the art is not articulated either expressly or inherently. As such, the outstanding rejection fails to satisfy all elements required for a finding of obvious as required under the analysis defined in Graham and reaffirmed in KSR. Applicant's remarks *infra* address each of the Graham elements and the rationale for a conclusion of obviousness.

Graham Factual Findings and Response Thereto

Wagner fails to teach or suggest dividing a sample having a protein or virus component into a plurality of aliquots or applying said plurality of aliquots in parallel to a first separation step to yield a plurality of partially resolved eluates. As such, applicant respectfully traverses the assertion that Wagner teaches all elements for which the reference is cited.

Wagner is cited as teaching: "a process for analyzing proteins in a sample comprising dividing a sample into plurality of aliquots (page 810, right column, 5th and 6th full paragraph)." (Paper No. 20080721, page 2.) Applicant respectfully traverses the assertion that Wagner teaches dividing a sample into a plurality of aliquots.

Wagner teaches that a single sample is applied to a RAM column. The RAM column is the first column used in Wagner. There is no teaching or suggestion of dividing the sample prior to application to the RAM column. The cited portion of Wagner at page 810, right column, 5th and 6th full paragraph merely speaks to obtaining the sample and cleanup procedure, not to dividing a sample into aliquots. Even if the CCL-153 cells are considered the sample and the separation into a plurality of aliquots is considered to be the result of removal of a 2-ml portion to be used for separation, it is only this 2 ml portion that is separated: i.e. only a single aliquot—not a plurality as required by the following element in the claim. Further, there is only one RAM column (page 811, Chromatographic Conditions; Fig. 1). The application to the RAM column

is in a single addition. Importantly, the RAM column is eluted step-wise. (page 811, Chromatographic Conditions) A person having ordinary skill in the art recognizes that a step elution results in total elution of the column. There is no identified teaching in Wagner of elution of the RAM column being done in aliquots. Finally, the RAM column is merely sample cleanup- no separation. (page 810, right column last paragraph in introduction.) A single fraction is important to the subsequent loading of the ion exchange column. This is seen in that Wagner teaches that the RAM column is directly connected in line with the IEX column. (page 812, left column, first full paragraph.)

Wagner is further cited as teaching "applying to a first separation step to yield a plurality of partially resolved eluates." (Paper No. 20080721, page 2.) However, Wagner's first separation step includes only a single column. (See Fig. 1) The IEX column is the first separation step in Wagner. There is only a single IEX column in the system of Wagner. ("*First Dimension*. The analytical anion exchange column." Page 811, right column.) In combination with Fig. 1 this demonstrates only a single column taught or suggested by Wagner for a first separation step.

No plurality of aliquots is applied to a first separation step in Wagner. More importantly, the obtaining the sample uses only a single column (page 810, right column, 6th paragraph), the RAM is only a single column, and the IEX is only a single column. Thus, whatever step is considered the first separation step, Wager does not teach or suggest that the step is done with a plurality of columns in parallel.

Wagner is cited as deficient in teaching:

that the mass spectrometry is performed on an orthogonal MALDI mass spectrometer, digesting a plurality of partially resolved eluates with a proteolytic enzyme to yield a plurality of digested eluates, labeling a sample with tagged or machine-readable labels, applying a plurality of aliquots in parallel to first separation step by a robot.” (Paper No. 20080721, page 3.)

As each of these elements are directed only to claims 7, 14, 21, 28, 32, and 33, Applicant interprets the outstanding rejection of claims 1-6, 8-12, 15-19, 21, 22, 24-25, 27, 30-31, and 34 as obvious solely over the teachings of Wagner.

To bolster the failings of Wagner, Paper No. 2008021 cites Gygi as teaching

a method of protein analysis comprising tryptic digestion of samples before separated by chromatography (page 9393, right column, 1st full paragraph, line 8) in mass spectrometry for protein identification (abstract), and suggests to develop novel techniques that permit large-scale (automation) quantitative comparison of protein expression (page 9395, right column, end of Conclusions). (Paper No. 20080721, page 4.)

Applicant respectfully traverses the assertion that Gygi suggests developing novel techniques that permit large-scale (automation) quantitative comparison of protein expression. The cited portion of Gygi must be read in light of the entire reference. This portion of the conclusions refers to a requirement found in Gygi to overload a gel with sample protein so as to detect low abundance proteins. Gygi teaches:

However, it is now apparent that the 2DE-MS/MS approach is unsuitable to detect, identify, and quantify every protein in a sample, a task that seems necessary for the comprehensive analysis and eventual mathematical description of biological processes and systems. For this reason, it is necessary to develop novel techniques that allow for much increased starting amounts while permitting large-scale quantitative comparison of protein expression. (Page 9395, right column, Conclusions.)

A person of ordinary skill in the art recognizes that this cited teaching of Gygi is directed to overloading a gel to identify low abundance proteins and does not speak to any teaching or suggestion of automation. Indeed, a person of ordinary skill in the art recognizes that the techniques of Gygi of using a gel as a first separation step whereby the lane containing protein is physically cut out prior to tryptic digestion is not amenable to automation. (see page 9393, right column, 1st full paragraph.)

To bolster the failings of Wagner to teach or suggest affixing a machine-readable label to at least one collection selected from the group in claim 33, Paper No. 20080721 cites Kachman as teaching “a method of protein analysis by tagging protein in fraction in mass mapping method four interlysate comparison of protein expression . . . and its potential to be automated.” (Paper No. 20080721, page 4.)

Applicant respectfully traverses the assertion that Kachman teaches or suggests affixing a machine readable label. The person of ordinary skill in the art when analyzing Kachman recognizes that the “tag” of Kachman does not represent the machine readable label affixed to any of a plurality of aliquots, a plurality of resolved eluates, or a plurality of resolved fractions. The “tag” of Kachman is merely an identifier assigned to a protein of particular molecular weight and pI for subsequent comparison to proteins in subsequent assays. Nothing is actually tagged, and the label is not taught or suggested to be machine readable. Kachman fails to teach or suggest that a label is machine readable or affixed to any of the elements of claim 33.

Each of the pending claims comprises elements that are neither taught nor suggested by the cited plurality of prior art. Applicant reserves the right to expressly identify all such additional deficiencies in the course of prosecution as necessary.

Resolution of One of Ordinary Skill in the Art

Part of the *Graham* factual inquiry requires an indication of the level of ordinary skill in the art to which the invention pertains. Within the outstanding Office Action, as such, it is respectfully requested that the level of ordinary skill in the art be stated with greater specificity as the present invention is submitted to require skills beyond those imparted to a single person of ordinary skill in the art. Upon identification of the level of ordinary skill in the art, Applicant reserves the right to make of record additional declarations provided under 37 CFR 1.132 detailing how particular claimed aspects are beyond the scope of various such professional individuals such as a biological chemist or protein biologist.

Rationale for Obviousness

The Supreme Court and the Court of Appeals for the Federal Circuit are in agreement that the teaching, suggestion, and motivation test as used by the CAFC is fully consistent with an analysis of obviousness under Graham. The Court in KSR articulated that “[t]here is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis,” and explained that the CAFC has, in many cases, applied the TSM test in accord with the principles of Graham. KSR, 127 S. Ct. at 1732, 82 USPQ2d at 1396. The Supreme Court also commented that the CAFC “no doubt has applied the test in accord with these principles [set forth in KSR] in many cases.” Id.

The CAFC has interpreted KSR to require an explicit showing that the prior art would

have suggested making the specific modifications necessary to achieve the claimed invention. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., the CAFC continued application of the teaching, suggestion, and motivation test “flexibly applied” so as to require that any *prima facie* case of obviousness must be accompanied by an explicit showing where the relied on prior art provided the requisite teaching, suggestion, or motivation. 520 F.3d 1358, 1364-65 (Fed. Cir. 2008). The flexible nature of the test allows for a teaching, suggestion, or motivation to arise from knowledge in the art or from a standard desire to improve on prior inventions. However, if the cited prior art is limited to patents and publications as it is in the subject rejection, and does not draw on additional sources such as general knowledge in the art, the teaching, suggestion, or motivation to modify that prior art must be found therein and this teaching, suggestion, or motivation must be made explicit. The prior art of record fails to provide, explicitly or inherently, any teaching, suggestion, or motivation that would lead a person having ordinary skill in the art to the instantly claimed invention.

The BPAI also recognized that KSR “held that the TSM test must be applied flexibly, and take into account a number of factors ‘in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed.’” Ex parte Whalen II, Appeal 2007-4423, July 23, 2008, page 15 (citing KSR Int’l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007)). Further, “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does . . . To facilitate review, this analysis should be made explicit.” Id. Finally, in the face of evidence that a reference teaches away from the claimed invention the BPAI stated “it must be shown that those of ordinary skill in the art would have had some apparent reason to

modify the known composition in a way that would result in the claimed composition.” Ex parte Whalen II, Appeal 2007-4423 at 16. Taken in sum, the BPAI recognizes that any *prima facie* case of obviousness must explicitly identify where any of multiple cited prior art provides motivation to combine the references so as to produce the claimed invention. This test is not met by the subject rejection in that the prior art of record fails to provide, explicitly or inherently, any teaching, suggestion, or motivation to combine the references so as to lead a person having ordinary skill in the art to the instantly claimed invention.

The standard set down in KSR is fully in line with historical precedent. As supported by the CAFC, there must be an express evidentiary showing of where the prior art provides motivation to combine all elements of the claims. It is a well established legal principle that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Additionally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). This suggestion or motivation must be made explicit. A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

In support of the above precedents, the Court in KSR suggested seven possible rationales for a finding of obviousness. These are captured in the Federal Register, 2007, Vol. 72, No. 195, 56525-56534, which serves as the current basis used by the USPTO for a finding of obviousness. These rationales are reproduced below.

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) “Obvious to try”—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

(Federal Register, Vol. 72, No. 195, 57529).

The basis of the rejection is:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Wagner by digesting and tagging protein samples in each fraction to analyze protein with MALDI mass spectrometer because Wagner teaches that multidimensional separation can be performed on digested protein (page 810, right column, 1st full paragraph) and Gygi teaches a digestion step in the mass spectrometer protein analysis. (Paper No. 20080721, page 4.)

The explanations articulated in Paper No. 20080721, lead Applicant to the assumption that the rationale for obviousness corresponds to rationale (A) of the KSR obviousness examination guidelines namely that the Examiner has found all prior art elements present in the

cited prior art and that they may be combined according to known methods to yield predictable results. In the event that Applicant's assumption as to the rationale for the rejection is incorrect, it is respectfully requested that the undersigned attorney of record be contacted at the earliest possible convenience so that a response may be provided consistent with the implicit rationale for the finding of obviousness. The requirements for an obviousness rejection based on this rationale are reproduced below.

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

To support the rejection under this rationale all prior art elements must be found explicitly in the cited prior art with the only deficiency being that there is not an actual combination of the elements in a single prior art reference. This requirement is fully in line with historical precedent that all elements must be taught or suggested in the cited prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Each element of the pending claims is not explicitly identified or present in the cited prior art such that *prima facie* case of obviousness under this rationale is not satisfied. Examiners attention is directed to the remarks *supra* that Wagner, Gygi, and Kachman fail to teach or suggest the elements for which they are cited.

As the cited prior art fails to teach or suggest all elements of the pending claims, applicant submits that the cited motivation for combination is in question. A person of ordinary skill in the art would not expect success in the use of an on-line array fractionation for mass spectrometry by using the tagging method of Kachman because that tagging method of Kachman is talks merely to be suitable for full-length undigested proteins.

Additionally, person of ordinary skill in the art has no reasonable expectation from the teaching of Gygi that separation may occur by lowering trip ticket digestion because Gygi does not teach or suggest multi dimensional separation of tryptic digested protein as stated in the outstanding rejection. (Paper No. 20080721, page 4.)

Perhaps most telling is that Gygi teaches away from dividing the sample because they were unsuccessful with low sample amounts. They needed to overload the gel with 50 mg of protein. (See page 9393, right column, first full paragraph.) In contrast, Wagner uses only 5 mg starting protein. (See page 811 "2D-HPLC system") Should the sample of Gygi be aliquotted it reduces the protein amount loaded in each lane of the gel and renders the system of Gygi

unsuitable for its intended purpose. This is taught by Gygi in at page 9393, right column, first full paragraph where they state that lower protein amounts do not produce suitable identification and resolution of low abundance proteins. Thus, the combination of Wagner and Gygi Cannot be used to support the *prima facie* case of obviousness. In the face of evidence that a reference teaches away from the claimed invention the BPAI stated "it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition." Ex parte Whalen II, Appeal 2007-4423 at 16. Applicant submits that the cited prior art fails to explicitly express some apparent reason to combine the references.

In sum, a *prima facie* case of obviousness is not satisfied by the combination of Wagner, Gygi, and Kachman in that not all elements are taught or suggested by the cited prior art as required under rationale (A). Accordingly, Applicants respectfully request that this rejection of the claims under consideration be withdrawn.

Remarks directed to the rejection of claims 1-6, 8-11, 13, 26, and 33 under 35 U.S.C. § 103(a) as unpatentable over Wagner et al. in view of Miliotis et al. (J. Chromatography A 2000;886:99-110).

Reconsideration in withdrawal of the rejection of claims 1-6, 8-11, 13, 26, and 33 is respectfully requested because the cited prior art fails to teach or suggest all elements of the pending claims. Applicants hereby incorporate by reference all remarks *supra* that Wagner fails to teach or suggest all elements for which this reference is cited.

To bolster the deficiencies of Wagner, Milotis is cited as teaching “a process for analyzing proteins where the chromatographic separation is continuously transferred onto a plate as discrete spots (fractions/eluates) in a precise array pattern (abstract, lines 5-6).” (Paper No. 20080721, page 4.) As the teaching of Milotis is directed merely to claims 3, 13, and 26, Applicant recognizes at the rejection as two claims 1, 2, 4-6, 8-11, and 33 are dependent on elements taught were suggested by Wagner alone.

Applicant incorporates by reference all remarks that Wagner is deficient in teaching all elements of claims 1 and 15, and the claims that depend therefrom.

With regard to claim 13, Milotis is cited as teaching using a MALDI plate for collection of fractions. The cited portion of Milotis does not teach using a microplate for sample collection. Thus, the reference does not provide teaching or motivation to use a microplate. More importantly, Milotis merely is cited for and teaches sample collection, not separation. Indeed, a person of ordinary skill in the art recognizes that the impermeable surface of a MALDI plate cannot be used for separation. In MALDI the laser desorption, ionization, and transfer into a charged field in a flight tube produces separation of sample after leaving the plate. Thus, Milotis fails to provide the requisite teaching to support the deficiencies in Wagner respect to claim 13.

With regard to claim 26 Applicant respectfully requests that Examiner state with greater specificity where Milotis teaches or suggests any element of this claim. Applicant fails to find any teaching or suggestion in Milotis to support the deficiencies of Wagner with regard to any element of claim 26.

A *prima facie* case of obviousness is not satisfied by the combination of Wagner with Milotis in that not all elements are taught or suggested by the cited prior art as required under

rationale (A). Accordingly, Applicants respectfully request that this rejection of the claims under consideration be withdrawn.

Summary

Claims 1-19, 21, 22, 24-27, and 30-34 remain pending in the application. Each of these claims is submitted to be in patentable form and directed to allowable subject matter. Reconsideration and withdrawal of the rejections and the passing of this application to allowance are requested. Should the Examiner have any suggestion as to how to improve the form of any of the pending claims, it is respectfully requested that the undersigned attorney be contacted at the telephone number provided below to resolve any outstanding issues.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 07-1180.

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Respectfully submitted,

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